Remarks:

Claims 3, 4, 6-9, 14, 15, 17-20 and 22-24 remain for consideration in this application.

In the office action dated January 7, 2005, claims 1, 3, and 12 were objected to. Applicants submit that these objections have been obviated in view of the claim amendments presented above and request that these objections be withdrawn.

Claims 1, 3-10, 12, 14-20, and 22-24 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner did note, however, that the present specification was enabling for a method to determine the presence of an ACE-inhibitor drug in a serum for a urine sample. Applicants have amended independent claims 1 and 12 to recite that the present inventive method is limited to determining the presence of ACE-inhibiting drugs present in a serum or urine sample obtained from a patient. Applicants request that the §112, first paragraph, rejections be withdrawn.

Claims 1, 3-10, 12, 14-20 and 22-24 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants respectfully disagree that the term "active" in claims 1 and 12 is indefinite. Applicants direct the Examiner's attention to page 7, lines17-21, of the specification. A definition is set forth for the term "active drug" which encompasses therapeutically active drugs as taken as well as drugs which have changed in structure before becoming therapeutically active. The term also encompasses metabolites that are therapeutically active. In addition, the preambles of claims 1 and 12 clearly set forth what an active drug is. As noted in the preambles, an active drug

is capable of modifying the activity level of an enzyme on a selected substrate. Therefore, the metes and bounds of the term "active drug" is plainly and succinctly set forth both in the claims themselves as well as in the specification. Applicants respectfully request that this rejection be withdrawn.

The Examiner also indicated that claims 1 and 12 were very confusing as it is difficult to understand how one would be able to determine the presence of a drug based on the standard activity from another *patient* sample. The determination of ACE-inhibiting drugs as presently claimed does not rely upon a standard activity from another single patient sample. Rather, the claims require that the standard activity level is established by testing samples from a plurality of individuals other than the patient. Applicants have amended claims 1 and 12 to further clarify that the standard is prepared by taking samples from a plurality of individuals. By using plural samples, random variations between individuals are averaged out over the entire group. Thus, concerns over whether enzyme activity from individual test samples are inhibited or enhanced are lessened considerably.

In the present claims, the measured activity level of the enzyme on the selected substrate is compared to a standard that is prepared by testing samples from a plurality of individuals, and not just a single individual. Applicants believe that this interpretation is clear from the present claim language in conjunction with the specification. Applicants respectfully request that the rejection under §112, second paragraph, be withdrawn.

Claims 1-6 were rejected under 35 U.S.C. §102(b) as being anticipated by Weinshilboum et al. As claim 1 has been amended to recite that the drug being tested for is an ACE-inhibiting drug, Weinshilboum et al. no longer anticipates claims 1-6. As the Examiner recognizes, Weinshilboum et al. is directed toward examination of the activity of erythrocyte (RBC) thiopurine

methyltransferase, an enzyme that catalyzes thiopurine S methylation. Thiopurines are drugs used in the treatment of patients with neoplastic and autoimmune diseases. Therefore, Applicants request that the §102(b) rejection to Weinshilboum et al. be withdrawn.

Claims 1-7, 10, 12, 14-18, and 20 were rejected under 35 U.S.C. §102(b) as being anticipated by Alegret et al. It is the Examiner's position that the three drugs (all of which are statins) with which the rabbits were treated in Alegret et al. are ACE-inhibitors. Applicants respectfully submit that statins are not ACE-inhibiting drugs as the Examiner purports. Applicants have attached hereto an article from MedicineNet.com that describes exactly what statins are. According to the article, statins are a class of drugs that lowers the level of cholesterol in the blood by reducing the production of cholesterol by the liver. In contrast, ACE-inhibiting drugs prevent the cleavage of angiotensin I to angiotensin II, thereby reducing blood pressure. Therefore, it is clear that Alegret et al. cannot anticipate independent claims 1 and 12. Applicants request that the §102(b) rejection by Alegret et al. be withdrawn.

Claims 1, 3-10, 12, 14-20, and 22-24 were rejected under 35 U.S.C. §103(a) as being obvious over Weinshilboum et al. in view of Alegret et al. and further in view of Brunner et al. It is the Examiner's position that it would have been obvious to modify/combine Weinshilboum et al's teachings according to the teachings from Alegret et al. and Brunner et al. to obtain the instantly claimed method because Alegret et al. teach a method to measure ACE activity as a function of ACE-inhibitor dosage in fluid samples obtained from a patient who may or may not be on an ACE-inhibitor and compare said ACE activity with a standard curve constructed on the basis of ACE activity measurements in a fluid sample from another patient. As Applicants have pointed out above,

Alegret et al. do not teach evaluation of ACE activity as a function of ACE-inhibitor dosage. Rather, Alegret et al. is directed toward the use of statins and their effect on cholesterol level. As ACE-inhibiting drugs combat hypertension by reducing blood pressure, there can be no analogy between statins and ACE-inhibiting drugs. Furthermore, the method of Brunner et al. uses a "standard" activity level that is a baseline reading from the same individual providing the fluid sample for enzyme activity level measurement post drug ingestion. This is clearly outside the scope of independent claims 1 and 12 which require that the standard activity level be established by testing samples from plural individuals other than the patient. Applicants request that the rejection under § 103(a) be withdrawn.

Any additional fee which is due in connection with this amendment should be applied against our Deposit Account No. 19-0522.

In view of the foregoing, a Notice of Allowance appears to be in order and such is courteously solicited.

Respectfully submitted,

By________________

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ATTORNEYS FOR APPLICANT(S)

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Written by Pharmacists
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Statins

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What are statins, and how do they work?

"Statins" are a class of drugs that lowers the level of cholesterol in the blood by reducing the production of cholesterol by the liver. Statins block the enzyme in the liver that is responsible for making cholesterol. This enzyme is called hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase for short). Scientifically, statins are called HMG-CoA reductase inhibitors.

Cholesterol is critical to the normal function of every cell in the body. However, it also contributes to the development of atherosclerosis, a condition in which cholesterol-containing plaques form within the arteries. These plaques block the arteries and reduce the flow of blood to the tissues the arteries supply. When plaques rupture, a blood clot forms on the plaque, thereby further blocking the artery and reducing the flow of blood. When blood flow is reduced sufficiently in the arteries that supply blood to the heart, the result is angina (chest pain) or a heart attack. If the clot occurs on plaques in the brain, the result is a stroke. Clots occurring on plaques in the leg cause intermittent claudication (pain in the legs while walking). By reducing the production of cholesterol, statins are able to reduce the formation of new plaques and occasionally can reduce the size of plaques that already exist. In addition, through mechanisms that are not well understood, statins also stabilize plaques and make them less prone to rupturing and forming clots.

Although the important role of cholesterol in atherosclerosis is widely accepted by scientists, research also shows that atherosclerosis is a complex process that involves more than just cholesterol. For example, scientists have discovered that inflammation in the walls of the arteries may be an important factor in atherosclerosis. New research shows that statins reduce inflammation, which could be another mechanism by which statins beneficially affect atherosclerosis. This reduction of inflammation does not depend on statins' ability to reduce cholesterol. Further, these anti-inflammatory effects can be seen as early as two weeks after starting statins.

For what conditions are statins used?

Statins are used for preventing and treating atherosclerosis that causes chest pain, heart attacks, strokes, and intermittent claudication in individuals who have or are at risk for atherosclerosis. Risk factors for atherosclerosis include abnormally elevated cholesterol levels, a family history of heart attacks (particularly at a young age),

increasing age, and diabetes. Most individuals are placed on statins because of high levels of cholesterol. Though cholesterol reduction is important, heart disease is complex and, as discussed previously, other factors such as inflammation may play a role. Thirty-five percent of individuals who develop heart attacks do not have high blood cholesterol levels, yet most of them have atherosclerosis. This means that high levels of cholesterol are not always necessary for atherosclerotic plaques to form.

Because it is not clear which effect of statins is responsible for their benefits, the goal of treatment with statins should not be only the reduction of cholesterol to normal levels, but rather the prevention of the complications of atherosclerosis-angina, heart attacks, stroke, intermittent claudication, and death. This concept is important because it allows for individuals who have or are at risk for atherosclerosis, but do not have high levels of cholesterol, to be considered for treatment with statins. Statins, like ACE inhibitors, are an important class of drugs because some of these drugs have been shown to reduce the incidence of heart attacks, strokes, and death.

Are there differences among statins?

Statins differ in several ways. The most obvious difference is in their ability to reduce cholesterol. Currently, atorvastatin (Lipitor) is the most potent and fluvastatin (Lescol) is the least potent. A new statin, rosuvastatin (Crestor), which is under development, may be more potent than atorvastatin. The statins also differ in how strongly they interact with other drugs. For example, pravastatin levels in the body are less likely to be elevated by other drugs because the enzymes in the liver that eliminate pravastatin (unlike the enzymes that eliminate other statins) are not blocked by most other drugs. Another difference is that only three of the statins--pravastatin, simvastatin, and lovastatin--have been shown in large studies to actually reduce heart attacks. In addition, simvastatin and pravastatin have demonstrated the ability to reduce death. Pravastatin also reduces the occurrence of strokes. Interestingly, these three statins are derived from natural sources and have similar chemical structures. The other statins are completely synthetic and have chemical structures that differ greatly from the natural statins.

Statins differ in the frequency with which they cause a rare side effect called rhabdomyolysis, in which muscles are damaged. Cerivastatin (Baycol) was withdrawn from pharmacies worldwide because it causes rhabdomyolysis more often than other statins. In contrast, the results from three large studies of pravastatin and over ten years of experience with pravastatin have proven that pravastatin is safe. Finally, statins also differ in how they affect fibrinogen, a protein that is important in the clotting of blood and the growth of smooth muscle cells (which, like inflammation, also may be involved in atherosclerosis). The importance of this difference is unclear. However, in view of the complexity of the process of atherosclerosis and the possibility that the beneficial effects of statins are due to effects other than their lowering of cholesterol, these differences could be quite important. Moreover, since it is not yet clear exactly how statins bring about their beneficial effects, it is important to demonstrate that each statin reduces heart attacks, strokes, and deaths in addition to comparing their effects. One such study now underway is comparing the effects of pravastatin and atorvastatin in reducing heart attacks, strokes, and death.

What are the side effects of statins?

Statins have few important side effects. The most common side effects are headache, nausea, vomiting, constipation, diarrhea, headache, rash, weakness, and muscle pain. The most serious (but fortunately rare) side effects are liver failure and rhabdomyolysis. Rhabdomyolysis is a serious side effect in which there is damage to muscles. Rhabdomyolysis often begins as muscle pain and can progress to loss of muscle cells, kidney failure, and death. It occurs more often when statins are used in combination with other drugs that themselves cause rhabdomyolysis or with drugs that prevent the elimination of statins and raise the levels of statins in the blood. Since rhabdomyolysis may be fatal, unexplained joint or muscle pain that occurs while taking statins should be brought to the attention of a healthcare provider for evaluation.

With which drugs do statins interact?

Statins have some important drug interactions. The first type of interaction involves the elimination of statins by the liver. Liver enzymes (specifically the cytochrome P-450 liver enzymes) are responsible for eliminating all statins from the body with the exception of pravastatin. Therefore, drugs that block the action of these liver enzymes increase the levels of simvastatin, lovastatin, fluvastatin, and atorvastatin (but not pravastatin) in the blood and can lead to the development of rhabdomyolysis. Drugs or agents that block these enzymes include

protease inhibitors (used in treating AIDS), erythromycin, itraconazole, clarithromycin, diltiazem, verapamil, and grapefruit juice. Another important drug interaction occurs between statins and niacin or fibric acids, e.g., gemfibrozil (Lopid), clofibrate (Atromid-S), and fenofibrate (Tricor). Fibric acids and niacin can cause rhabdomyolysis or liver failure when used alone and combining them with statins increases the likelihood of rhabdomyolysis or liver failure. Nevertheless, fibric acids and niacin are often used with caution in combination with most statins. Cholestyramine (Questran) as well as colestipol (Colestid) bind statins in the intestine and reduce their absorption into the body. To prevent this binding within the intestine, statins should be taken one hour before or four hours after cholestyramine or colestipol.

Which statins are available?

Statins that are approved for use in the United States include lovastatin (Mevacor), simvastatin (Zocor), pravastatin (Pravachol), atorvastatin (Lipitor), fluvastatin (Lescol), and rosuvastatin (Crestor).

Last Editorial Review: 1/31/2005

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